A Phase I/II clinical trial of pNGVL4a-Sig/E7(detox)/HSP70 for the treatment of patients with HPV16+ Cervical Intraepithelial Neoplasia 2/3 (CIN2/3)

Non-technical abstract

Cervical cancer is the third leading cause of cancer death in women worldwide. In the United States, despite the availability of inexpensive, noninvasive screening, cervical cancer remains the sixth most commonly diagnosed malignancy among women. Over the past decade, SEER[1] data have demonstrated a 17% increase in incidence in the U.S., normalized for population growth, with a disproportionate increase among young women. Current primary therapies include radical surgery and chemoradiation. For those with recurrent disease, a combination of further surgery including total pelvic exenteration, radiation, and chemotherapy may be used. However these modalities are associated with significant treatment toxicity, and overall survival remains a dismal 40%. One of the best strategies to decrease the disease burden of cervical cancer is to intervene in patients with premalignant disease of the cervix. The identification of the association of high-risk strains of human papillomavirus (HPV) with premalignant disease of the cervix provides an ideal opportunity to develop vaccines targeted at HPV+ premalignant lesions. HPV16 is associated with over half of all cervical cancers and precursor lesions (CIN2/3). The DNA vaccine we propose to evaluate, pNGVL4a-Sig/E7(detox)/HSP70, is targeted at the HPV16 E7 protein, which is consistently expressed in cancerous and precancerous epithelial cells, but not in normal tissue.

Current therapy for Cervical Intraepithelial Neoplasia

Treatments for cervical dysplasia are ablative, such as cryotherapy, laser vaporization, or cone procedures. All current therapeutic options are destructive, have adverse sequelae, and furthermore are not always curative. Among treated HSILs in immunocompetent women, the overall risk of recurrence is less than ten percent when all surgical margins are clear. This risk increases to approximately 25% in women with positive endocervical margins. About 90% of recurrences will occur within the first year after treatment. Women who have undergone cervical conization have three times the risk of cervical stenosis as those who have not. Several authors have documented a significantly increased risk of premature delivery in pregnancies subsequent to cervical conization, and subsequent neonatal low birth weight. Moreover, tissue destruction from therapeutic interventions can make subsequent detection and treatment of recurrent disease more difficult, as the healing process tends to draw the transition zone of the cervical epithelium proximally, into the endocervical canal. While these complications are not insurmountable, effective immunotherapy would obviate the need for surgery, to say nothing of preventing progression to cervical cancer.

Treatment vaccines for HPV disease

Treatment vaccines, or immunotherapies, are a potential type of treatment for HPV disease. Therapeutic vaccines are based on the idea that the immune system can be activated to destroy cancerous or precancerous cells. In the case of HPV disease, the goal is to make a vaccine that would activate the immune system to destroy only cells infected with HPV. The vaccine we are testing is a DNA plasmid vaccine that is targeted at the HPV16 E7 protein. This protein is consistently expressed in cervical cancers and cervical cancer precursor lesions, CIN2/3.

[1] SEER: Surveillance, Epidemiology and End Results

HPV Vaccine Clinical Trial

Study patients will receive a total of three vaccinations with the experimental vaccine before undergoing standard therapeutic surgical resection of any remaining abnormal cervical tissue, at week 15. A total of 31 patients will be enrolled in the trial. Eligibility criteria will include healthy women with biopsy-confirmed CIN2/3 caused by HPV16. Vaccinations will be spaced four weeks apart. Patients will also undergo an interval colposcopic examination at week 8 to make sure that their cervical lesion is not getting worse. Blood samples and cervical swabs will be taken at several time points, to measure immune responses. The trial requires a total of 6 visits over a five-month period.

These samples will be taken at the time of study visits. Patients will also be asked to report any side effects, such as injection site discomfort, on diary cards. The endpoints of the phase I portion of the trial include safety, toxicity, and tolerability assessments based on NCI CTC v3.0. The endpoints for the phase II portion of the clinical trial include comparing immune responses to vaccination with any clinical responses we might see.